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Previously Undescribed Form of B-Cell Chronic Lymphoid Leukemia With IgA Expression/Secretion and Lytic Bone Lesions

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A B-cell chronic lymphoid leukemia (B-CLL) associated with IgA expression and secretion is uncommon and has never been described in association with osteolytic bone lesions. We report such a case, defined by cytomorphology and flow cytometric immunophenotyping (FCI). Additional cases may be recognized with the aid of FCI, in order to define the natural history of and best form of therapy for this rare disorder. Am. J. Hematol. 55:208–211, 1997. © 1997 Wiley-Liss, Inc.

B-cell chronic lymphoid leukemia; IgA; osteolysis

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is composed predominantly of small, round, mature lymphocytes. It is most commonly of B-cell origin (>90% of all CLL) with the following immunophenotype: CD5+, CD19+, CD20+, CD23+ CD10−, faint sIgM+, and sIgD+/− [1]. The abnormal lymphocytes in CLL ordinarily have receptors for a single type of light chain and for heavy chains of IgM or IgD. The latter may co-exist or be present with receptors for IgM or IgD [2]. In addition to monoclonal surface expression, approximately 5% of patients with CLL will have a prominent monoclonal immunoglobulin ''peak'' in their plasma, sharply visible against the background of hypogammaglobulinemia [3–11]. Monoclonal gammopathies are most often of the IgM type, but IgG or IgA M components may also occur, much less often [12].

Bone lesions occur relatively uncommonly in CLL with diffuse demineralization being the most common skeletal aberration in CLL, affecting 5% of patients. Osteolytic lesions are distinctly uncommon and pathologic fractures are rare. A syndrome of osteolytic bone lesions, hypercalcemia, and monoclonal light chain secretion has been observed rarely in patients with well-differentiated sIgM+ B-CLL [13–15]. There are no previous reports demonstrating a well-differentiated sIgA+ B-CLL with osteolytic bone lesions, monoclonal light chain secretion, and monoclonal serum IgA/kappa.

We report a previously undescribed form of B-cell chronic lymphoid leukemia, defined by morphology and flow cytometric immunophenotyping, associated with osteolytic bone lesions, a marked serum monoclonal IgA, and urinary free kappa light chains associated with slight hyperviscosity. The patient was treated with VAD (vincristine, adriamycin, and decadron) with a decrease in the serum IgA level.

CASE REPORT

A 72-year-old white man presented with a 3-month history of vague, general malaise, a 5-pound weight loss, and arthritic-type pains in his feet. Physical examination revealed no lymphadenopathy nor organomegaly. A complete blood count (CBC) revealed a white blood cell count (WBC) of 26,400/μl (86% lymphocytes, 11% segmented neutrophils, 1% band forms, and 2% monocytes), a hemoglobin (Hgb) of 8.2 g/dl, and platelet count of

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85,000/μl. Serum total protein was elevated to 10.2 g/dl due to an increased gamma globulin (6.7 g/dl). Serum protein electrophoresis (SPE) revealed a prominent IgA monoclonal spike (IgA = 5,450 mg/dl, IgG = 233 mg/dl, and IgM = 10 mg/dl). Urine protein electrophoresis revealed a markedly elevated total protein of 1,620 mg/24 hr with 80% in the gamma golubin region; a monoclonal band was detected as were free kappa light chains by immunofixation. Serum uric acid was 12.4 mg/dl (normal, 2.5–7.7); serum calcium, 9.9 mg/dl (normal, 8.5–10.8); serum Beta 2-microglobulin, 9.0 mg/l (normal, <3); and serum viscosity, 3.0 (normal, 1.5–1.9). Serum cryoglobulins were not detected. Serum alkaline phosphatase was 55 U/L (normal, 25–140). Computerized axial tomographic (CT) scans of the chest, abdomen, and pelvis failed to reveal any lymphadenopathy or hepatosplenomegaly. Bone survey revealed innumerable lytic lesions with a moth-eaten appearance in the skull. A bone marrow aspiration and core biopsy were performed for morphologic and flow cytometric analysis. A diagnosis of ''atypical B-cell chronic lymphoid leukemia'' was made. The patient was initially treated with 2 cycles of chlorambucil (30 mg) and Prednisone (80 mg, daily and subsequently tapered). There was an associated slight decrease in serum IgA (4,300 mg/dl); however, there was a subsequent increase in the serum IgA and hypercalcemia ensued. The patient was then treated with 4 cycles of VAD (vincristine, 0.4 mg; adriamycin, 16 mg, daily, by continuous infusion, day 1–4; and decadron, 40 mg, daily, day 1–4). The serum IgA decreased markedly to 1,600 mg/dl. However, within the month following his 4th cycle of VAD, the patient presented with weakness, fatigue, confusion, and high fever. The patient had previously expressed a desire to have no further therapy. The patient continued to deteriorate, was placed on Hospice, and died.

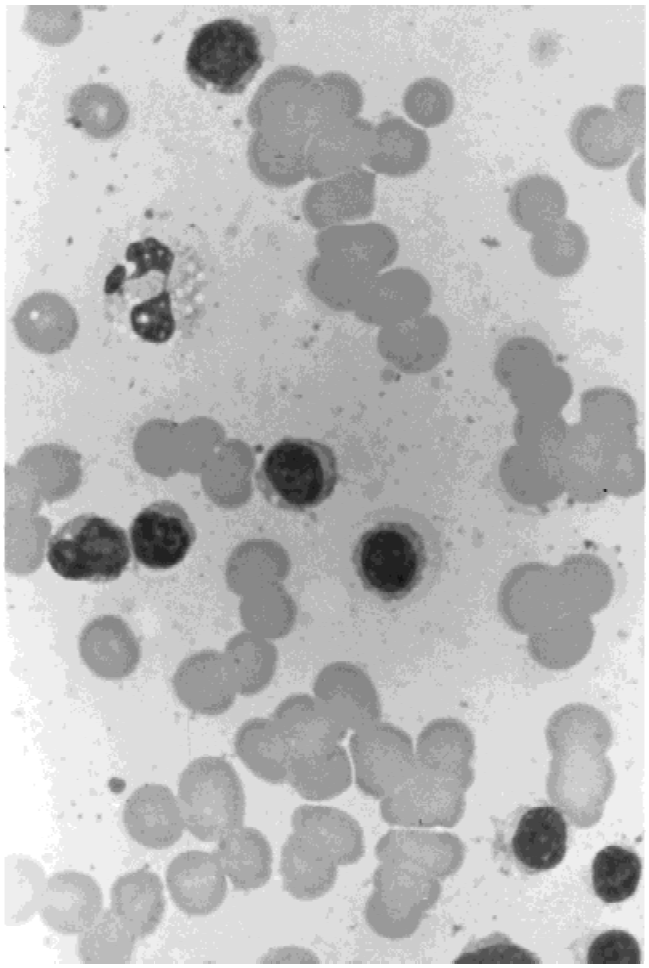

Fig. 1. Bone marrow aspirate smear with small, mature lymphocytes (Wright's stain, ×1,000).

MATERIALS AND METHODS

Light Microscopy/Immunohistochemistry

Peripheral blood and bone marrow aspirate smears were Wright's-stained. The bone marrow core biopsy was stained with hematoxyline and eosin (H&E) as well as kappa and lambda immunoperoxidase stains using BioGenex Super Sensitive Multilink-Alkaline Phosphatase Immunodetection System (San Ramon, CA).

Flow Cytometry

A bone marrow aspirate was analyzed on a FACSCAN (Becton Dickinson, Mountainview, CA) flow cytometer for various atnigens using standard techniques and commercially available monoclonal antibodies, including CD3, CD4, CD45 (Becton-Dickinson), CD5, CD8 (Gen Trak, Wayne, PA), CD10, CD14 (MY4), CD19, CD20, CD25, CD56 (Coulter Clone, Coulter Immunology, Hialeah, FL), CD11c, CD23 (DAKO, Carpinteria, CA), HLA-DR (Ortho-Diagnostic Systems, Raritan, NJ), and IgA, IgD, IgG, IgM, kappa and lambda (Kallestad, Inc., Chaska, MN).

RESULTS

Light Microscopy/Immunohistochemistry

Review of the Wright's-stained peripheral blood smear revealed an increase in small, round, mature lymphocytes. Minimal rouleaux formation was present. Review of the Wright's-stained bone marrow aspirate smear revealed a markedly hypercellular (75%) marrow with sheets of small lymphocytes with a clumped nuclear chromatin pattern, round nuclear borders, and scant cytoplasm. Nucleoli were not present and there was not a significant proportion of large cells. Plasmacytoid lymphocytes and plasma cells were not present (Fig. 1). The H&E stained bone marrow core biopsy revealed 75% cellularity with approximately 90% of the marrow cellularity composed of small, round lymphocytes without

plasmacytoid features. Morphologically, this would be classified as FAB subtype, chronic lymphocytic leukemia of the typical type [16]. Kappa and lambda immunoperoxidase staining of the core biopsy revealed selective cytoplasmic membrane staining of the small lymphocytes with kappa. Cytoplasmic staining and plasma cells were not identified with kappa and lambda staining.

Flow Cytometry

Flow cytometric analysis of the bone marrow revealed a markedly hypercellular specimen (198,500/μl) with 87% of cells within the lymphocyte region, 4% within the monocyte region, and 9% within the granulocyte region. This represented marked expansion of the lymphocyte region. Cells within the lymphocyte region were composed of 98% monoclonal B cells with expression of CD45, CD20, CD23, and IgA/kappa of a dim intensity. Of interest, the monoclonal B cells were not expressing CD19, HLA-DR, and, in addition, were not expressing CD5, CD10 (Calla), CD11c or CD25. Cells within the monocyte region were composed of 93% of cells with the same monoclonal B cell immunophenotype. Thus, flow cytometric analysis detected that this monoclonal B cell population represented 91% of the bone marrow cellularity.

DISCUSSION

B-cell CLL is defined as a proliferation of small, mature appearing cells that exhibit expression of CD19, CD20, CD23, HLA-DR, CD5, and weak monoclonal surface immunoglobulin light chains. Our patient presented with a lymphocytosis composed of small, round, mature lymphocytes with a monoclonal B-cell immunophenotype (CD45+, CD20+, CD23+, and IgA/kappa+). The cells were aberrant with no expression of CD19 or HLA-DR. In addition, they did not express CD5, a T-cell marker commonly expressed in B-CLL; infrequent cases (7%) of B-CLL do not have aberrant CD5 expression [17–18]. Leukemic cells in CD5-negative cases otherwise had the same morphology and immunophenotype as CD5+ B-cell in the report of Ikematsu et al. [18]. Of interest, there was an associated serum and urinary IgA monoclonal protein with urinary free kappa light chains. There was an associated slight serum hyperviscosity, secondary to the highly elevated serum IgA level. However, morphologically, there were no features of a lymphoplasmacytic malignancy.

Osteolytic bone lesions of the skull were also identified in this patient. This finding is distinctly uncommon in B-CLL and is more commonly seen in lymphoplasmacytic disorders, including Waldendrom's macroglobulinemia, and in multiple myeloma. Rare cases of B-CLL with osteolytic bone lesions have been described [13–15]; however, in these rare cases, in lymphoplasmacytic disorders, and in multiple myeloma (MM), hypercalcemia is common and may be secondary to increased serum immunoreactive parathormone (iPTH) or osteoclast activating factor (OAF) [19,20]. These levels were not measured in our case.

The serum Beta-2-microglobulin (B-2M) was elevated in the present patient. B-2M, a low molecular weight protein, is a component of class I HLA molecules, and may be increased in the serum of a variety of lymphoproliferative disorders, including MM and non-Hodgkin's lymphomas [21].

The present case represents a previously undescribed form of B-CLL, defined by morphology and flow cytometric immunophenotyping. The clinical features are more typical of a lymphoplasmacytic disorder or MM and suggest an unusual mature B-cell (nonplasmacytic) proliferation with secretory and osteolytic capabilities. Although leukeran or fludarabine are considered conventional, front-line therapy for CLL, the patient was treated with a chemotherapeutic regimen which would be appropriate for MM and CLL, due to the clinical features. There was no documented subsequent development of a plasmacytic malignancy (i.e., plasma cell leukemia or multiple myeloma) or a lymphoplasmacytic malignancy. Flow cytometric immunophenotyping may allow further recognition of such cases in order to define their natural history and determine the best form of therapy. Serum B-2M levels may be useful as an indicator of disease response, as in MM, and may be evaluated as additional cases are recognized.

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